Search Strategy

FILE 'MEDLINE' ENTERED AT 22:50:39 ON 22 JUN 2003

		E	SHOJI S/AU
		E	E10
L1	7	S	E5
L2	131782	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3	2128	S	L2 AND (CXCR4 OR CCR5)
L4	33	S	L3 AND (CYCLIC)
L5	63	S	L3 AND (EXTRACELLULAR LOOP OR EXTRACELLULAR DOMAIN)
L6	38	S	L5 AND (SECOND EXTRACELLULAR LOOP OR EXTRACELLULAR LOOP 2 OR

FILE 'USPATFULL' ENTERED AT 23:18:23 ON 22 JUN 2003

		E	SHOJI SHOZO/IN
L7	6	S	E2 OR E3
L8	24988	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9	634	S	L8 AND (CXCR4 OR CCR5)
L10	286	S	L9 AND (CYCLIC)
L11	99	S	L10 AND (EXTRACELLULAR LOOP OR EXTRACELLULAR DOMAIN)
L12	5	S	L11 AND (SECOND EXTRACELLULAR LOOP OR EXTRACELLULAR LOOP 2 OR

FILE 'WPIDS' ENTERED AT 23:21:28 ON 22 JUN 2003

		E	SHOJI SHOZO/IN
L13	55	S	E1
L14	0	S	L13 AND (CXCR4 CCR5)
L15	15446	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L16	209	S	L15 AND (CXCR4 OR CCR5)
L17	10	S	L16 AND (EXTRACELLULAR LOOP OR EXTRACELLULAR DOMAIN)

2,3,4,6,7,

L4 ANSWER 15 OF 33 MEDLINE
2001653913 Document Number: 21548292. PubMed ID: 11689643. A cyclic dodecapeptide-multiple-antigen peptide conjugate from the undecapeptidyl arch (from Arg(168) to Cys(178)) of extracellular loop 2 in CCR5 as a novel human immunodeficiency virus type 1 vaccine. Misumi S; Nakajima R; Takamune N; Shoji S. (Department of Biochemistry, Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto 862-0973, Japan.) JOURNAL OF VIROLOGY, (2001 Dec) 75 (23) 11614-20. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A cyclic closed-chain dodecapeptide (cDDR5) mimicking the conformation-specific domain of CCR5 was prepared in which Gly-Asp, as a dipeptide forming a spacer arm, links the amino and carboxyl termini of the decapeptidyl linear chain (Arg(168) to Thr(177)) derived from the undecapeptidyl arch (UPA; Arg(168) to Cys(178)) of extracellular loop 2 (ECL2) in CCR5. Novel monoclonal antibodies were raised against cDDR5 conjugated with a multiple-antigen peptide (cDDR5-MAP), and the purified antibody [KB8C12, immunoglobulin M(kappa)] reacted with cDDR5, but not with linear DDR5, in real-time biomolecular interaction analysis using surface plasmon resonance. The antibody also reacted with cells expressing CCR5, but not with cells expressing CXCR4, and the immunoreaction was competed by cDDR5-MAP. The antibody significantly interfered with chemotaxis induced by macrophage inflammatory protein, 1beta, and at a concentration of 1.67 nM it almost completely inhibited infection by human immunodeficiency virus type 1 (HIV-1) R5, but not by HIV-1 X4, as observed by use of a new phenotypic assay for drug susceptibility of HIV-1 using the CCR5-expressing HeLa CD4(+) cell clone 1-10 (MAGIC-5). Furthermore, cDDR5-MAP suppressed infection by HIV-1 R5 at relatively high concentrations (50 to 400 microM) in a dose-dependent manner but did not suppress infection by HIV-1 X4. Taken together, these results indicate that the antibody is conformation specific and recognizes the conformation-specific domain of the UPA of ECL2. Moreover, both the antibody and its immunogen, the cDDR5-MAP conjugate, may be useful in developing a new candidate vaccine for HIV therapy.

L4 ANSWER 19 OF 33 MEDLINE
2001431426 Document Number: 21371752. PubMed ID: 11478800. Evidence as a HIV-1 self-defense vaccine of cyclic chimeric dodecapeptide warped from undecapeptidyl arch of extracellular loop 2 in both CCR5 and CXCR4. Misumi S; Takamune N; Ido Y; Hayashi S; Endo M; Mukai R; Tachibana K; Umeda M; Shoji S. (Department of Biochemistry, Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, 862-0973, Japan.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Aug 3) 285 (5) 1309-16. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Novel conformation-specific antibodies were raised against a cyclic chimeric dodecapeptidyl multiple antigen peptide (cCD-MAP) constructed with a spacer-armed Gly-Asp dipeptide and two pentapeptides (S(169)-Q(170)-K(171)-E(172)-G(173) of CCR5 and E(179)-A(180)-D(181)-D(182)-R(183) of CXCR4) which are components of the undecapeptidyl arch (UPA: from R(168) to C(178) in CCR5, from N(176) to C(186) in CXCR4) of extracellular loop 2 (ECL2) in chemokine receptors (CCR5 and CXCR4). Of the antibodies raised, one monoclonal antibody, CPMAb-I (IgMkappa), reacted with cCD-MAP, but not with the linear chimeric dodecapeptide-MAP. The antibody reacted with the cells separately expressing CCR5

or CXCR4, but not with those not expressing the coreceptors. Moreover, the antibody markedly suppressed infection by X4, R5, or R5X4 virus in a dose-dependent manner in a new phenotypic assay for drug susceptibility of HIV-1 using CCR5-expressing Hela/CD4(+) cell clone 1-10 (MAGIC-5). Moreover, CPMAb-I interfered with LAV-1(BRU) infection (m.o.i. = 0.01) of Molt4#8 cells cocultured with CPMAb-I-producing hybridoma in the transwell, and significantly interfered with neither chemotaxis nor calcium influx induced with stromal cell-derived factor 1 alpha (SDF-1alpha). Thus, the antibody raised against the cCD-MAP provides powerful protection or defense against HIV-1 infection. We therefore propose the cCD-MAP or its derivative immunogen as a novel candidate for an HIV-1 coreceptor-based self-defense vaccine.

L6 ANSWER 11 OF 38 MEDLINE
2001491410 Document Number: 21425397. PubMed ID: 11531415. Adaptation to blockade of human immunodeficiency virus type 1 entry imposed by the anti-CCR5 monoclonal antibody 2D7. Aarons E J; Beddows S; Willingham T; Wu L; Koup R A. (Department of Medicine, Division of Infectious Disease, University of Texas Southwestern Medical Center, Texas, Dallas 75390, USA.) VIROLOGY, (2001 Sep 1) 287 (2) 382-90. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The second extracellular loop (ECL2) domain of CC-chemokine receptor 5 (CCR5) has been proposed as a specific target site for therapeutic agents aimed at blocking CCR5 -dependent entry by human immunodeficiency virus type I (HIV-1). We have adapted two CCR5 -using HIV-1 isolates, prototypic JR-CSF, and a primary isolate, 11-121, to replicate in vitro in the presence of high concentrations of a monoclonal antibody (MAb 2D7) specific for the CCR5 ECL2 domain. The 75% inhibitory concentrations (IC(75)) for the two 2D7-adapted isolates were approximately 100-fold higher than those for corresponding control isolates passaged without the MAb. Adapted isolates did not acquire the ability to use CXCR4, CCR3, or CCR1. Env clones derived from MAb 2D7-adapted JR-CSF showed several gp120 mutations that were not found in any of the control JR-CSF clones. The in vitro observations suggest that CCR5-using HIV-1 strains might also be able to adapt in vivo to evade an ECL2-blocking therapeutic agent.

L6 ANSWER 21 OF 38 MEDLINE
1999214354 Document Number: 99214354. PubMed ID: 10196311. Differential inhibition of human immunodeficiency virus type 1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5. Olson W C; Rabut G E; Nagashima K A; Tran D N; Anselma D J; Monard S P; Segal J P; Thompson D A; Kajumo F; Guo Y; Moore J P; Maddon P J; Dragic T. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA.) JOURNAL OF VIROLOGY, (1999 May) 73 (5) 4145-55. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The CC-chemokine receptor CCR5 mediates fusion and entry of the most commonly transmitted human immunodeficiency virus type 1 (HIV-1) strains. We have isolated six new anti-CCR5 murine monoclonal antibodies (MAbs), designated PA8, PA9, PA10, PA11, PA12, and PA14. A panel of CCR5 alanine point mutants was used to map the epitopes of these MAbs and the previously

described MAb 2D7 to specific amino acid residues in the N terminus and/or second extracellular loop regions of CCR5. This structural information was correlated with the MAbs' abilities to inhibit (i) HIV-1 entry, (ii) HIV-1 envelope glycoprotein-mediated membrane fusion, (iii) gp120 binding to CCR5, and (iv) CC-chemokine activity. Surprisingly, there was no correlation between the ability of a MAb to inhibit HIV-1 fusion-entry and its ability to inhibit either the binding of a gp120-soluble CD4 complex to CCR5 or CC-chemokine activity. MAbs PA9 to PA12, whose epitopes include residues in the CCR5 N terminus, strongly inhibited gp120 binding but only moderately inhibited HIV-1 fusion and entry and had no effect on RANTES-induced calcium mobilization. MAbs PA14 and 2D7, the most potent inhibitors of HIV-1 entry and fusion, were less effective at inhibiting gp120 binding and were variably potent at inhibiting RANTES-induced signaling. With respect to inhibiting HIV-1 entry and fusion, PA12 but not PA14 was potently synergistic when used in combination with 2D7, RANTES, and CD4-immunoglobulin G2, which inhibits HIV-1 attachment. The data support a model wherein HIV-1 entry occurs in three stages: receptor (CD4) binding, coreceptor (CCR5) binding, and coreceptor-mediated membrane fusion. The antibodies described will be useful for further dissecting these events.

L6 ANSWER 24 OF 38 MEDLINE

1999173969 Document Number: 99173969. PubMed ID: 10074122. Identification of CXCR4 domains that support coreceptor and chemokine receptor functions. Doranz B J; Orsini M J; Turner J D; Hoffman T L; Berson J F; Hoxie J A; Peiper S C; Brass L F; Doms R W. (Department of Pathology and Laboratory Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) JOURNAL OF VIROLOGY, (1999 Apr) 73 (4) 2752-61. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The interaction of the chemokine stromal cell-derived factor 1 (SDF-1) with its receptor CXCR4 is vital for cell trafficking during development, is capable of inhibiting human immunodeficiency virus type 1 (HIV-1) utilization of CXCR4 as a coreceptor, and has been implicated in delaying disease progression to AIDS in vivo. Because of the importance of this chemokine-chemokine receptor pair to both development and disease, we investigated the molecular basis of the interaction between CXCR4 and its ligands SDF-1 and HIV-1 envelope. Using CXCR4 chimeras and mutants, we determined that SDF-1 requires the CXCR4 amino terminus for binding and activates downstream signaling pathways by interacting with the second extracellular loop of CXCR4. SDF-1-mediated activation of CXCR4 required the Asp-Arg-Tyr motif in the second intracellular loop of CXCR4, was pertussis toxin sensitive, and did not require the distal C-terminal tail of CXCR4. Several CXCR4 mutants that were not capable of binding SDF-1 or signaling still supported HIV-1 infection, indicating that the ability of CXCR4 to function as a coreceptor is independent of its ability to signal. Direct binding studies using the X4 gp120s HXB, BH8, and MN demonstrated the ability of HIV-1 gp120 to bind directly and specifically to the chemokine receptor CXCR4 in a CD4-dependent manner, using a conformationally complex structure on CXCR4. Several CXCR4 variants that did not support binding of soluble gp120 could still function as viral coreceptors, indicating that detectable binding of monomeric gp120 is not always predictive of coreceptor function.

L6 ANSWER 25 OF 38 MEDLINE
1999173949 Document Number: 99173949. PubMed ID: 10074102. Effect of mutations in the second extracellular loop of CXCR4 on its utilization by human and feline immunodeficiency viruses. Brelot A; Heveker N; Adema K; Hosie M J; Willett B; Alizon M. (INSERM U.332, Institut Cochin de Genetique Moleculaire, 75014 Paris, France.) JOURNAL OF VIROLOGY, (1999 Apr) 73 (4) 2576-86. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB CCR5 and CXCR4 are the principal CD4-associated coreceptors used by human immunodeficiency virus type 1 (HIV-1). CXCR4 is also a receptor for the feline immunodeficiency virus (FIV). The rat CXCR4 cannot mediate infection by HIV-1NDK or by FIVPET (both cell line-adapted strains) because of sequence differences with human CXCR4 in the second extracellular loop (ECL2). Here we made similar observations for HIV -189.6 (a strain also using CCR5) and for a primary HIV -1 isolate. It showed the role of ECL2 in the coreceptor activity of CXCR4 for different types of HIV-1 strains. By exchanging ECL2 residues between human and rat CXCR4, we found that several amino acid differences contributed to the inactivity of the rat CXCR4 toward HIV-189.6. In contrast, its inactivity toward HIV-1NDK seemed principally due to a serine at position 193 instead of to an aspartic acid (Asp193) in human CXCR4. Likewise, a mutation of Asp187 prevented usage of CXCR4 by FIVPET. Different mutations of Asp193, including its replacement by a glutamic acid, markedly reduced or suppressed the activity of CXCR4 for HIV-1NDK infection, indicating that the negative charge was not the only requirement. Mutations of Asp193 and of arginine residues (Arg183 and Arg188) of CXCR4 reduced the efficiency of HIV-1 infection for all HIV -1 strains tested. Other ECL2 mutations tested had strain-specific effects or no apparent effect on HIV-1 infection. The ECL2 mutants allowed us to identify residues contributing to the epitope of the 12G5 monoclonal antibody. Overall, residues with different charges and interspersed in ECL2 seem to participate in the coreceptor activity of CXCR4. This suggests that a conformational rather than linear epitope of ECL2 contributes to the HIV-1 binding site. However, certain HIV-1 and FIV strains seem to require the presence of a particular ECL2 residue.

L6 ANSWER 26 OF 38 MEDLINE
1999107834 Document Number: 99107834. PubMed ID: 9890944. A critical site in the core of the CCR5 chemokine receptor required for binding and infectivity of human immunodeficiency virus type 1. Siciliano S J; Kuhmann S E; Weng Y; Madani N; Springer M S; Lineberger J E; Danzeisen R; Miller M D; Kavanaugh M P; DeMartino J A; Kabat D. (Merck Research Laboratories, Immunology and Rheumatology, Rahway, New Jersey 07065, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jan 22) 274 (4) 1905-13. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Like the CCR5 chemokine receptors of humans and rhesus macaques, the very homologous (approximately 98-99% identical) CCR5 of African green monkeys (AGMs) avidly binds beta-chemokines and functions as a coreceptor for simian immunodeficiency viruses. However, AGM CCR5 is a weak coreceptor for tested macrophage-tropic (R5) isolates of human immunodeficiency virus type 1 (HIV-1). Correspondingly, gp120 envelope glycoproteins derived from R5 isolates of HIV-1 bind poorly to AGM

CCR5. We focused on a unique extracellular amino acid substitution at the juncture of transmembrane helix 4 (TM4) and extracellular loop 2 (ECL2) (Arg for Gly at amino acid 163 (G163R)) as the likely source of the weak R5 gp120 binding and HIV-1 coreceptor properties of AGM CCR5. Accordingly, a G163R mutant of human CCR5 was severely attenuated in its ability to bind R5 gp120s and to mediate infection by R5 HIV-1 isolates. Conversely, the R163G mutant of AGM CCR5 was substantially strengthened as a coreceptor for HIV-1 and had improved R5 gp120 binding affinity relative to the wild-type AGM CCR5. These substitutions at amino acid position 163 had no effect on chemokine binding or signal transduction, suggesting the absence of structural alterations. The 2D7 monoclonal antibody has been reported to bind to ECL2 and to block HIV-1 binding and infection. Whereas 2D7 antibody binding to CCR5 was unaffected by the G163R mutation, it was prevented by a conservative ECL2 substitution (K171R), shared between rhesus and AGM CCR5s. Thus, it appears that the 2D7 antibody binds to an epitope that includes Lys-171 and may block HIV-1 infection mediated by CCR5 by occluding an HIV-1-binding site in the vicinity of Gly-163. In summary, our results identify a site for gp120 interaction that is critical for R5 isolates of HIV-1 in the central core of human CCR5, and we propose that this site collaborates with a previously identified region in the CCR5 amino terminus to enable gp120 binding and HIV-1 infections.

L6 ANSWER 27 OF 38 MEDLINE

1998389858 Document Number: 98389858. PubMed ID: 9721247. Interactions among HIV gp120, CD4, and CXCR4: dependence on CD4 expression level, gp120 viral origin, conservation of the gp120 COOH- and NH2-termini and V1/V2 and V3 loops, and sensitivity to neutralizing antibodies. Mondor I; Moulard M; Ugolini S; Klasse P J; Hoxie J; Amara A; Delaunay T; Wyatt R; Sodroski J; Sattentau Q J. (Case 906, The Centre d'Immunologie de Marseille-Luminy, Marseille Cedex 9, 13288, France.) VIROLOGY, (1998 Sep 1) 248 (2) 394-405. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The binding of HIV-derived recombinant soluble (s)gp120 to the CD4(+)/CXCR4(+) A3.01 T cell line inhibits the binding of the CXCR4-specific monoclonal antibodies 12G5, which interacts with the second extracellular loop, and 6H8, which binds the NH2 terminus. We have used this as an assay to analyse the interaction of recombinant sgp120 from diverse viral origins with CXCR4. The strength of the interaction between sgp120 and CXCR4 correlated with sgp120 affinity for the CD4-CXCR4 complex, and the interaction of sgp120MN and sgp120IIIB with CXCR4 was highly dependent on the level of CD4 expressed on a variety of different T cell lines. sgp120 from X4, R5X4, and R5 viruses interacted with CXCR4, although the R5 sgp120-CXCR4 interactions were weaker than those of the other gp120s. The interaction of sgp120IIIB or sgp120MN with CXCR4 was inhibited by neutralizing monoclonal antibodies that prevent the sgp120-CD4 interaction but also by antibodies specific for the gp120 V2 and V3 loops, the CD4-induced epitope and the 2G12 epitope, which interfere weakly or not at all with CD4-sgp120 binding. The binding to A3.01 cells of wild-type sgp120HxB2, but not of sgp120 deleted in the COOH and NH2 termini, interfered with 12G5 binding in a dose-dependent manner. Further deletion of the V1 and V2 loops restored CXCR4 binding activity, but additional removal of the V3 loop eliminated the gp120-CXCR4 interaction, without decreasing the affinity between mutated sgp120 and CD4. Taken together, these results demonstrate that the interactions between sgp120 and

CXCR4 are globally similar to those previously observed between sgp120 and CCR5, with some apparent differences in the strength of the sgp120-CXCR4 interactions and their dependence on CD4. Copyright 1998 Academic Press.

L6 ANSWER 33 OF 38 MEDLINE
97477421 Document Number: 97477421. PubMed ID: 9334377. Interaction of chemokine receptor CCR5 with its ligands: multiple domains for HIV-1 gp120 binding and a single domain for chemokine binding. Wu L; LaRosa G; Kassam N; Gordon C J; Heath H; Ruffing N; Chen H; Humblias J; Samson M; Parmentier M; Moore J P; Mackay C R. (LeukoSite, Inc., Cambridge, Massachusetts 02142, USA.. lijun_wu@leukosite.com) . JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Oct 20) 186 (8) 1373-81. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB CCR5 is a chemokine receptor expressed by T cells and macrophages, which also functions as the principal coreceptor for macrophage (M)-tropic strains of HIV-1. To understand the molecular basis of the binding of chemokines and HIV-1 to CCR5, we developed a number of mAbs that inhibit the various interactions of CCR5, and mapped the binding sites of these mAbs using a panel of CCR5/CCR2b chimeras. One mAb termed 2D7 completely blocked the binding and chemotaxis of the three natural chemokine ligands of CCR5, RANTES (regulated on activation normal T cell expressed and secreted), macrophage inflammatory protein (MIP)-1alpha, and MIP-1beta, to CCR5 transfectants. This mAb was a genuine antagonist of CCR5, since it failed to stimulate an increase in intracellular calcium concentration in the CCR5 transfectants, but blocked calcium responses elicited by RANTES, MIP-1alpha, or MIP-1beta. This mAb inhibited most of the RANTES and MIP-1alpha chemotactic responses of activated T cells, but not of monocytes, suggesting differential usage of chemokine receptors by these two cell types. The 2D7 binding site mapped to the second extracellular loop of CCR5, whereas a group of mAbs that failed to block chemokine binding all mapped to the NH2-terminal region of CCR5. Efficient inhibition of an M-tropic HIV -1-derived envelope glycoprotein gp120 binding to CCR5 could be achieved with mAbs recognizing either the second extracellular loop or the NH2-terminal region, although the former showed superior inhibition. Additionally, 2D7 efficiently blocked the infectivity of several M-tropic and dual-tropic HIV -1 strains in vitro. These results suggest a complicated pattern of HIV-1 gp120 binding to different regions of CCR5, but a relatively simple pattern for chemokine binding. We conclude that the second extracellular loop of CCR5 is an ideal target site for the development of inhibitors of either chemokine or HIV-1 binding to CCR5.

L6 ANSWER 34 OF 38 MEDLINE
97460076 Document Number: 97460076. PubMed ID: 9312096. The second extracellular loop of CCR5 is the major determinant of ligand specificity. Samson M; LaRosa G; Libert F; Paindavoine P; Detheux M; Vassart G; Parmentier M. (Institute of Interdisciplinary Research, Universite Libre de Bruxelles, Campus Erasme, 808 route de Lennik, B-1070 Bruxelles, Belgium.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Oct 3) 272 (40) 24934-41. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The chemokine receptor CCR5 binds macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, and regulated on activation, normal T-cell expressed and secreted (RANTES), and constitutes the major

co-receptor allowing infection of CD4(+) T lymphocytes, macrophages, and microglial cells by macrophage-tropic strains of human and simian immunodeficiency virus. CCR5 is most closely related to CCR2b, another chemokine receptor that responds to monocyte chemoattractant protein (MCP)-1, MCP-2, MCP-3, and MCP-4. We have investigated by mutagenesis the regions of CCR5 and CCR2b involved in the specificity of binding and functional response to their respective ligands. We demonstrate that the key region of CCR5 involved in its specific interaction with MIP-1alpha, MIP-1beta, and RANTES, and its subsequent activation, lies within the second extracellular loop (and possibly the adjacent transmembrane segments). Conversely, the NH2-terminal domain of CCR2b is responsible for the high affinity binding of MCP-1, but is not sufficient to confer activation of the intracellular cascades. Extracellular loops of the receptor, among which the second loop plays a prominent role, are necessary to achieve efficient signaling of the receptor. These data complement our previous mapping of CCR5 domains functionally involved in the fusion process with the human immunodeficiency virus envelope, and will help in the development of agents able to interfere with the early steps of viral infection.

L6 ANSWER 36 OF 38 MEDLINE
97322389 Document Number: 97322389. PubMed ID: 9177234. Evolution of HIV-1 coreceptor usage through interactions with distinct CCR5 and CXCR4 domains. Lu Z; Berson J F; Chen Y; Turner J D; Zhang T; Sharron M; Jenks M H; Wang Z; Kim J; Rucker J; Hoxie J A; Peiper S C; Doms R W. (James Graham Brown Cancer Center, University of Louisville, Louisville, KY 40202, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Jun 10) 94 (12) 6426-31. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The chemokine receptor CXCR4 functions as a fusion coreceptor for T cell tropic and dual-tropic HIV-1 strains. To identify regions of CXCR4 that are important for coreceptor function, CXCR4-CXCR2 receptor chimeras were tested for the ability to support HIV-1 envelope (env) protein-mediated membrane fusion. Receptor chimeras containing the first and second extracellular loops of CXCR4 supported fusion by T tropic and dual-tropic HIV-1 and HIV-2 strains and binding of a monoclonal antibody to CXCR4, 12G5, that blocks CXCR4-dependent infection by some virus strains. The second extracellular loop of CXCR4 was sufficient to confer coreceptor function to CXCR2 for most virus strains tested but did not support binding of 12G5. Truncation of the CXCR4 cytoplasmic tail or mutation of a conserved DRY motif in the second intracellular loop did not affect coreceptor function, indicating that phosphorylation of the cytoplasmic tail and the DRY motif are not required for coreceptor function. The results implicate the involvement of multiple CXCR4 domains in HIV-1 coreceptor function, especially the second extracellular loop, though the structural requirements for coreceptor function were somewhat variable for different env proteins. Finally, a hybrid receptor in which the amino terminus of CXCR4 was replaced by that of CCR5 was active as a coreceptor for M tropic, T tropic, and dual-tropic env proteins. We propose that dual tropism may evolve in CCR5 -restricted HIV-1 strains through acquisition of the ability to utilize the first and second extracellular loops of CXCR4 while retaining the ability to interact with the CCR5 amino-terminal domain.

L17 ANSWER 8 OF 10 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-466075 [40] WPIDS
DNN N2000-347870 DNC C2000-140427
TI Identifying agents which inhibit interaction of CD4 and CCR5, useful for prevention and treatment of viral infections, comprises contacting cell with agent such as antibody.
DC B04 D16 S03
IN DIMITROV, D S; XIAO, X
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 90
PI WO 2000040964 A1 20000713 (200040)* EN 67p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000027226 A 20000724 (200052)
ADT WO 2000040964 A1 WO 2000-US417 20000106; AU 2000027226 A AU 2000-27226 20000106
FDT AU 2000027226 A Based on WO 200040964
PRAI US 1999-115182 19990108

AB WO 200040964 A UPAB: 20000823
NOVELTY - A method (I) for identifying an agent which inhibits the interaction of CD4 and CCR5 in a cell, is new and comprises contacting a cell which expresses CD4 and CCR5 with an agent, evaluating the interaction and comparing it to that of a control cell, where a decreased interaction indicates the ability of the agent to inhibit infection with an immunodeficiency virus.
ACTIVITY - Virucide; anti-HIV.
MECHANISM OF ACTION - Inhibits the interaction of CD4 and CCR5 which is important for Envelope protein mediated membrane fusion.
USE - (I) is useful for identifying an agent which inhibits the interaction of CD4 and CCR5 in a cell. The agent identified is useful for preventing or inhibiting infection of a cell with an immunodeficiency lentivirus type 1 (HIV-1) and may be administered to treat a subject having or at risk of having an immunodeficiency virus infection (all claimed).
Dwg.0/5

L17 ANSWER 9 OF 10 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-431480 [37] WPIDS
DNC C2000-131148
TI Preventing and treating human immunodeficiency virus (HIV) infections using compounds that inhibit interactions between HIV and its fusion co-receptor, especially antibodies specific for the CCR5 chemokine receptor.
DC B04 D16
IN MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 29
PI WO 2000035409 A2 20000622 (200037)* EN 68p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX
AU 2000021996 A 20000703 (200046)
EP 1144006 A2 20011017 (200169) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

JP 2002538771 W 20021119 (200281) 65p
ADT WO 2000035409 A2 WO 1999-US30345 19991216; AU 2000021996 A AU 2000-21996 19991216; EP 1144006 A2 EP 1999-966466 19991216, WO 1999-US30345 19991216; JP 2002538771 W WO 1999-US30345 19991216, JP 2000-587730 19991216
FDT AU 2000021996 A Based on WO 200035409; EP 1144006 A2 Based on WO 200035409; JP 2002538771 W Based on WO 200035409
PRAI US 1998-212793 19981216; US 1998-112532P 19981216

AB WO 200035409 A UPAB: 20000807
NOVELTY - A composition (I) for inhibiting human immunodeficiency virus (HIV)-1 infection, comprising at least 2 synergistic compounds (especially antibodies specific for chemokine receptor CCR5) for inhibiting HIV infection, is new. At least 1 of the compounds prevents productive interaction between HIV-1 and a HIV-1 fusion co-receptor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method (II) for treating a subject infected with HIV -1, or preventing a subject becoming infected, comprising administering (I);

(2) an anti-CCR5 monoclonal antibody (III), selected from PA8 (ATCC HB-12605), PA9 (ATCC HB-12606), PA10 (ATCC HB-12607), PA11 (ATCC HB-12608), PA12 (ATCC HB-12609) and/or PA14 (ATCC HB-12610);

(3) a nucleic acid molecule (IV) encoding the light chain from (III);

(4) a nucleic acid molecule (V) encoding the heavy chain from (III);

(5) a nucleic acid molecule (VI) encoding the Fab chain from (III);

(6) a nucleic acid molecule (VII) encoding the CDR (complementary determining region) from (VIII); and

(7) nucleic acid molecules (IX) encoding the variable region from (III).

ACTIVITY - Viricidal.

MECHANISM OF ACTION - Inhibition of interactions between HIV -1 and HIV-1 fusion co-receptors, especially antibody inhibition of CCR5 chemokine receptor binding.

HIV-1 envelope-mediated fusion between HeLa-EnvJR-FL+ and PM1 cells was detected using the RET (resonance energy transfer) assay. Equal numbers (2 multiply 104) of fluorescein octadecyl ester (F18)-labeled envelope expressing cells and octadecyl rhodamine (R18)-labeled PM1 cells were plated in 96-well plates in 15% fetal calf serum in DPBS (undefined) and incubated for 4 hours (h) at 37 deg. C in the presence of varying concentrations of the anti-CCR5 mAbs (monoclonal antibodies), PA8 to PA12, PA14, 2D7 or a non-specific murine IgG1. Fluorescence RET was measured with a Cytofluor (RTM) plate-reader and % RET was determined as described by Litwin V et al., HIV-1 membrane fusion mediated by laboratory adapted strain and a primary isolate analyzed by resonance energy transfer, J. Virol., 70:6437-6441.

NLluc+env- viruses complemented in trans by envelope glycoproteins from JR-FL or Gun-1 were produced as previously described by Dragic TV et al., Amino terminal substitutions in the CCR5 co-receptor impair gp120 binding and HIV-1 entry, J. Virol., 72:279-285. U87MG-CD4+ CCR5+ cells were infected with chimeric, reporter viruses containing 50-100 ng/ml p24 in the presence of varying concentrations of the individual mAbs. After 2h at 37 deg. C, virus-containing media were replaced by fresh, mAb-containing media. Fresh media, without antibodies, was added again after 12 h. After a total of 72h, 100 microliters of lysis buffer were added to the cells and luciferase activity (r.l.u.) was measured as described by Dragic et al., supra. The percentage inhibition of HIV-1 infection was defined as (1-(r.l.u in the presence of antibody / r.l.u in the absence of antibody)) x 100%.

All 6 mAbs and mAb 2D7 blocked fusion between CD4+CCR5+ PM1

cells and HeLa-EnvJR-FL+ cells in the RET assay. The descending rank order of potency was 2D7, PA14, PA12, PA11, PA10, PA9, PA8. The IC50 values for PA14 and 2D7 were 1.7 micrograms/ml and 1.6 micrograms/ml (respectively), for PA11 and PA12 is was 25.5 micrograms/ml and 10 micrograms/ml (respectively). PA8, PA9 and PA10 inhibited fusion by 10-15% at 300 micrograms/ml. None of the mAbs affected fusion between PM1 cells and HeLa-EnvLai+ cells which express the full length envelope protein from an X4 virus.

USE - (I) is used for preventing and treating infections caused by HIV-1 viruses (e.g. acquired immunodeficiency syndrome (AIDS)).

Dwg.0/6

L20 ANSWER 10 OF 54 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-487624 [52] WPIDS
CR 1995-382985 [49]; 1997-503105 [46]; 1998-286866 [25]; 1999-229499 [19]; 1999-229532 [19]; 1999-229533 [19]; 1999-254381 [21]; 1999-254713 [21]; 1999-302739 [25]; 1999-326705 [27]; 1999-337420 [28]; 1999-347718 [29]; 1999-371118 [31]; 1999-404743 [34]; 1999-430385 [36]; 1999-551358 [46]; 1999-580306 [49]; 1999-620728 [53]; 2000-038358 [03]; 2000-062031 [05]; 2000-072883 [06]; 2000-116314 [10]; 2000-237871 [20]; 2000-271386 [23]; 2000-271431 [23]; 2000-271434 [23]; 2000-271435 [23]; 2000-292842 [25]; 2000-317943 [27]; 2000-412154 [35]; 2000-412324 [35]; 2000-412325 [35]; 2000-431586 [37]; 2000-442668 [38]; 2000-452188 [39]; 2000-452395 [39]; 2000-499263 [44]; 2000-572269 [53]; 2000-572270 [53]; 2000-572271 [53]; 2000-587437 [55]; 2000-594320 [56]; 2000-594321 [56]; 2000-611443 [58]; 2000-611444 [58]; 2000-628263 [60]; 2000-638138 [61]; 2000-638201 [61]; 2000-679484 [66]; 2001-016509 [02]; 2001-025022 [03]; 2001-025251 [03]; 2001-025253 [03]; 2001-032160 [04]; 2001-050025 [06]; 2001-050091 [06]; 2001-070561 [08]; 2001-071075 [08]; 2001-071078 [08]; 2001-071395 [08]; 2001-081051 [09]; 2001-090793 [10]; 2001-091968 [10]; 2001-103149 [11]; 2001-183260 [18]; 2001-226690 [23]; 2001-226823 [23]; 2001-235264 [24]; 2001-381383 [40]; 2001-381384 [40]; 2001-408281 [43]; 2001-451708 [48]; 2001-541567 [60]; 2001-541628 [60]; 2001-602746 [68]; 2001-625876 [72]; 2002-075461 [10]; 2002-090516 [12]; 2002-130120 [17]; 2002-130151 [17]; 2002-130882 [17]; 2002-171999 [22]; 2002-172001 [22]; 2002-205567 [26]; 2002-256031 [30]; 2002-280917 [32]; 2002-280928 [32]; 2002-280940 [32]; 2002-292065 [33]; 2002-362426 [39]; 2002-383270 [41]; 2002-404358 [43]; 2002-657277 [70]; 2002-665999 [71]; 2002-673823 [72]; 2002-690475 [74]; 2002-713224 [77]; 2002-731348 [79]; 2002-740172 [80]; 2002-750461 [81]; 2003-066810 [06]; 2003-066893 [06]; 2003-066898 [06]; 2003-090845 [08]; 2003-102117 [09]; 2003-147434 [14]; 2003-147446 [14]; 2003-148238 [14]; 2003-155950 [15]; 2003-167072 [16]; 2003-174088 [17]; 2003-174140 [17]; 2003-174141 [17]; 2003-183819 [18]; 2003-183820 [18]; 2003-183821 [18]; 2003-183822 [18]; 2003-198285 [19]; 2003-201194 [19]; 2003-247083 [24]; 2003-275322 [27]; 2003-288106 [28]; 2003-288123 [28]; 2003-288142 [28]; 2003-288163 [28]; 2003-311003 [30]; 2003-328481 [31]; 2003-328482 [31]; 2003-328499 [31]; 2003-328612 [40]; 2003-328636 [31]; 2003-328637 [31]; 2003-328851 [40]; 2003-328860 [31]; 2003-329601 [31]; 2003-330485 [31]; 2003-331419 [31]; 2003-331420 [31]; 2003-331421 [31]; 2003-331422 [31]; 2003-340824 [32]; 2003-340981 [32]; 2003-341079 [32]; 2003-341189 [32]; 2003-341326 [32]; 2003-341327 [32]; 2003-341328 [32]; 2003-341502 [32]; 2003-341587 [32]; 2003-341588 [40]; 2003-341589 [32]; 2003-341590 [32]; 2003-341591 [32]; 2003-341713 [32]; 2003-341714 [32]; 2003-341840 [32]; 2003-352829 [33]; 2003-353471 [33]; 2003-353472 [33]; 2003-362213 [34]; 2003-370792 [35]; 2003-370797 [35]; 2003-393229 [37]; 2003-401699 [38]; 2003-401847 [38]; 2003-401848 [38]; 2003-401849 [38]; 2003-417250 [39]; 2003-417251 [39]; 2003-417252 [39]; 2003-417284 [39]
DNC C2002-138499
TI New cyclic peptides from human immune deficiency virus gp41, useful for treatment or prevention of HIV infection, are constrained to have alpha-helical conformation.

DC B04 D16
IN BRAISTED, A C; JUDICE, J K; MCDOWELL, R S; PHELAN, J C; STAROVASNIK, M A; WELLS, J A
PA (GETH) GENENTECH INC
CYC 1
PI US 6271198 B1 20010807 (200252)* 175p
ADT US 6271198 B1 CIP of US 1996-743698 19961106, Provisional US 1997-49787P 19970616, CIP of US 1997-876698 19970616, US 1997-965056 19971105
PRAI US 1997-49787P 19970616; US 1996-743698 19961106; US 1997-876698 19970616; US 1997-965056 19971105
AB **US 6271198 B UPAB: 20030619**
NOVELTY - Cyclic peptides (A) with a constrained helical conformation, derived from gp41 protein of human immune deficiency virus (HIV), are new.

DETAILED DESCRIPTION - The cyclic peptides of formulae (I), (VI), (XI) and (XVI) are new

S = macromolecule or is absent;
X = hydrogen or one or more amino acids (aa);
Y = hydroxy if S is absent, or it is one or more aa, or absent;
m and p = 0-6, totaling 6 or less;
n = an integer in the range (7-(m+p) to (9-(m+p)) but must be greater than 1;
q and v = 1-7;
s and t and v = 0-6, provided q+s or t+v is not over 7;
r = an integer in the range (7-(q+s) to (9-(q+s)) but is greater than zero;
u = an integer in the range (7-(t+v) to (9-(t+v)) but is greater than zero;
w and y = 1-7, totaling 8 or less;
x = an integer in the range (7-(w+y) to (9-(w+y)) but is equal to or greater than zero;
Z = sequence of 6 aa of form gabcde, defgab or cdefga, comprising six contiguous aa in: (i) the 633-678 region of gp41 from HIV-1LAI strain; (ii) its homolog in other HIV strains; or (iii) a consensus sequence of its homologs from any HIV clade, and its aa substituted variant, where aa 633, or corresponding aa in homolgs, is assigned position a of a repeating abcdefg assignment.

ACTIVITY - Virucide; Anti-HIV.
No details of tests for these activities are given.

MECHANISM OF ACTION - Induction of a specific immune response, resulting in antibodies that prevent virus-induced membrane fusion.

USE - (A) are used to treat subjects with, or at risk of, HIV infection, either as antifusion/anti-infection agents or, preferably where associated with a carrier, as an immunogen (including as vaccine) to raise antibodies (Ab). Ab may be used for diagnosis or prevention/treatment of HIV infection, e.g. prevention of mother-to-child transmission or in cases of health care accidents.

ADVANTAGE - (A) can be based on specific HIV strains, e.g. breakthrough isolates of HIV that have developed during vaccine trials, so a combination of them should cover a wide range of protection.
Dwg.0/23

L20 ANSWER 45 OF 54 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-198687 [25] WPIDS
DNC C1993-087944
TI Hybrid immunogens for treatment or prevention of HIV - comprise cyclic HIV principal neutralising determinant and synthetic analogue of E. Coli or S. Willmorei lipo-peptide.
DC B04
IN HANNAH, J; TOLMAN, R L
PA (MERI) MERCK & CO INC

CYC 9
PI EP 547681 A2 19930623 (199325)* EN 21p
R: CH DE FR GB IT LI NL
CA 2085083 A 19930619 (199336)
JP 05271276 A 19931019 (199346) 12p
EP 547681 A3 19940302 (199519)
ADT EP 547681 A2 EP 1992-203846 19921210; CA 2085083 A CA 1992-2085083 19921210; JP 05271276 A JP 1992-334730 19921215; EP 547681 A3 EP 1992-203846 19921210
PRAI US 1991-811047 19911218

AB **EP 547681 A** UPAB: 19931116
A hybrid immunogen is claimed comprising a cyclic HIV principal neutralising determinant (PND) and a synthetic lipopeptide analogue of the E. coli or S. willmorei lipopeptide.
The synthetic lipopeptide analogue may be, e.g., triacyl-cysteinyl-seryl-serine, (PAM)3CysSerSer. Pref. immunogens are of formula (I) (X3 is 1-25 aminoacids long, selected from the sequence of aminoacids found in any of the common isolates of HIV gp.120, amino-terminal and adjacent to the GlyProGlyArg sequence; X4 is a bond or 1-25 aminoacids long, selected from the sequence of aminoacids of any of the common isolates of HIV gp.120, carboxy-terminal and adjacent to the GlyProGlyArg sequence.
ADVANTAGE - The immunogens are useful for inducing B and T cell immune responses against the epitope expressed by the cyclic portion of the immunogen and are useful in the treatment or prevention of HIV infection.
Dwg.0/0

L20 ANSWER 47 OF 54 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-058511 [08] WPIDS
DNC C1992-026368
TI New cyclic HIV principal neutralising determinant peptide(s) - used as laboratory tools and as vaccines against HIV, AIDS, arc etc..
DC B03 B04 D16
IN BEDNAREK, M A; CHRISTENSE, B G; DOLAN, C A; SUGG, E E; TOLMAN, R L
PA (MERI) MERCK & CO INC
CYC 9
PI EP 471453 A 19920219 (199208)*
R: CH DE FR GB IT LI NL
CA 2047033 A 19920120 (199215)
JP 04243897 A 19920831 (199242) 15p
EP 471453 A3 19930310 (199349)
ADT EP 471453 A EP 1991-306582 19910719; JP 04243897 A JP 1991-179121 19910719; EP 471453 A3 EP 1991-306582 19910719
PRAI US 1990-555112 19900719

AB **EP 471453 A** UPAB: 19940126
A cyclic HIV Principal Neutralising Determinant (HIV-cPND) peptide of formula (I), or a salt, is new. WhereAA= amino acid, r = H, PhCH2OCO (Z), AcCys or AcCys(Acm), R1 = a bond or a peptide with 1-5 AA, opt. including a marker, R2 = a bond or a peptide of up to 17 AA if R3 = a peptide of at least 2 AA or a peptide of 2-17 AA if R3 = a bond, R3 = a bond to R7, or a peptide of up to 17 AA, if R2 = a peptide of at least 2 AA or a peptide of 2-17 AA if R2 = a bond, GPGR = GlyProGlyArg, R5 is bonded to a loop AA if R3 = a bond, or to R3 if R3 = an AA or a peptide, R5 = a peptide of 1-5 AA, a marker AA, OH, COOH, CONH2 or is absent, R7 = a bond, 1-8C alkylene (opt. substd. by 1 or 2 of NH2 or CONH2 and/or a hetero gp.) or CH2CH2CH(CONH2)NH, R8 = a bond

or 1-8C alkylene.

More speficially (I) has the formula (IA) or (IB), where X1 is selected from serine, proline, arginine, histidine, glutamine or threonine, X2 is selected from isoleucine, arginine, valine or methionine, X3 is selected from alanine, arginine or valine, X4 = phenylalanine, isoleucine or valine and Xm, Xn are constituents of R3 and R2 respectively, and = a bond or a peptide of up to 15 AA.

USE - (I) are stable HIV cPND peptides, which are useful as analytical tools and as reagents in ELISA assays. They are useful reagents for prepn. of conjugates having mammalian anti-peptide, anti-HIV or HIV neutralising immune responses, or to prepare compsns. for use as anti-HIV vaccines or as immunogens for treatment of HIV diseases including AIDs and ARC in humans. @(25pp Dwg.No.0/0 0/0

L20 ANSWER 49 OF 54 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-026506 [04] WPIDS
CR 1992-034437 [05]
DNC C1992-011395
TI New cyclic HIV principal neutralising determinant peptide(s) - comprising di sulphide bonds used as immunogens, analytical tools, conjugates used as vaccine for HIV and AIDS.
DC B04 D16
IN BONDY, S S; EMINI, E A; HANNAH, J; MARBURG, S; TOLMAN, R L
PA (MERI) MERCK & CO INC
CYC 14
PI EP 467701 A 19920122 (199204)*
R: AT BE CH DE ES FR GB IT LI LU NL SE
CA 2047078 A 19920120 (199215)
JP 04243896 A 19920831 (199242) 11p
JP 05260963 A 19931012 (199345) 51p
EP 467701 A3 19930310 (199349)
ADT EP 467701 A EP 1991-306599 19910719; JP 04243896 A JP 1991-179122 19910719; JP 05260963 A JP 1991-271683 19910719; EP 467701 A3 EP 1991-306599 19910719
PRAI US 1991-715127 19910619; US 1990-555558 19900719; US 1990-555974 19900719; US 1991-715275 19910619

AB **EP 467701 A** UPAB: 19971030
PND peptide is of formula (I) where r is H or (II); W is CH2CH2, CH2CH2CH2 or R6; R6 is (III)-(VI); R7 is lower alkyl, lower alkoxy or halo; R1 is a bond, or 1-5 aminoacid (AA) peptide, opt. incl. a marker AA; R2 and R3 are 3-10 AA peptides; R5 is OH, 1-5AA peptide or NH2; and R8 is a 1-8C lower alkyl. Also prepn. of (I) comprises preparing a linear, Acm-thiol protected peptide and reacting it with iodine, removing all AA protecting gps. and isolating the disulphide prod..

USE - Mfr. of a medicament for inducing anti-peptide, anti-HIV or HIV-neutralising antibodies (Abs) in a mammal. Used as a vaccine. Useful in the prevention and treatment of AIDS and AIDS related complex (ARC). @(22pp Dwg.No.0/0

L28 ANSWER 20 OF 79 MEDLINE
2000235259 Document Number: 20235259. PubMed ID: 10772633. Affinity and potency of proinhibitory antipeptide antibodies against CYP2D6 is enhanced using cyclic peptides as immunogens.
Schulz-Utermoehl T; Edwards R J; Boobis A R. (Section on Clinical Pharmacology, Division of Medicine, Imperial College School of Medicine, Hammersmith Campus, London, United Kingdom.) DRUG METABOLISM AND DISPOSITION, (2000 May) 28 (5) 544-51. Journal code: 9421550. ISSN: 0090-9556. Pub. country: United States. Language: English.

AB A series of antipeptide antibodies directed against CYP2D6 were produced by immunizing rabbits with peptides that were sterically unrestrained (linear) or conformationally restricted by cyclization. A variety of sites within the region comprising residues 254 to 290 of CYP2D6 were targeted. In immunoblotting studies, each of the antibodies against the linear and cyclic peptides recognized only a single immunoreactive band of 54 kDa in human liver microsomal fraction and bound to recombinant CYP2D6, but not recombinant CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, or CYP3A4. However, **the relative intensity of immunoreactive bands was considerably stronger for those antibodies raised against cyclic peptides**. Similarly, in an enzyme-linked immunosorbent assay, **antibodies raised against cyclic peptides bound 10 to 100 times more strongly to recombinant CYP2D6 than antibodies raised against the corresponding linear peptides**. None of the antibodies raised against linear peptides had any effect on debrisoquine 4-hydroxylase activity of human hepatic microsomal fraction; however, anticyclic peptide antibodies targeted against residues 254 to 273, 261 to 272, and 257 to 268 of CYP2D6 inhibited enzyme activity by a maximum of 60, 75, and 91%, respectively. In contrast, despite binding strongly to CYP2D6, an anticyclic peptide antibody directed against residues 278 to 290 did not inhibit enzyme activity. The epitope of the proinhibitory anticyclic peptide antibody directed against residues 257 to 268 of CYP2D6 included Thr-261 and Trp-262, and indicates a role for these residues in enzyme inhibition. In conclusion, **immunization with peptides conformationally restricted by cyclization to mimic loop regions of CYP2D6 resulted in strongly binding antibodies** that when targeted appropriately were able to inhibit CYP2D6-catalyzed activity.

L28 ANSWER 37 OF 79 MEDLINE
1998226417 Document Number: 98226417. PubMed ID: 9566765. Linear and cyclic peptides mimicking the disulfide loops in HIV-2 envelope glycoprotein induced antibodies with different specificity. Jrad B B; Bahraoui E. (Laboratoire d'Immuno-Virologie, Universite Paul Sabatier, Toulouse, France.) MOLECULAR IMMUNOLOGY, (1997 Nov-Dec) 34 (16-17) 1177-89. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The aim of this study was to compare the immunogenicity and antigenicity of cyclic and linear peptides that mimic the disulfide loops in HIV-2ROD gp125. Based on the hypothetical assignment of intrachain disulfide bonds in HIV-2 envelope glycoprotein, peptides expected to mimic all 11 disulfide-bonded domains were synthesized, oxidized or cysteine-alkylated; they were then purified and characterized. Rabbits were immunized with either linear cysteine-alkylated peptides (L1-L11) or cyclic oxidized peptides (C1-C11). All peptides except 7L elicited antibodies with titers between 10(3) and 5 x 10(6). Anti-peptide C (2, 3, 4, 7, 8, 9, 11) and anti-peptide L (2,

3, 8, 9, 11) antibodies recognized the native HIV-2 gp 125. Moreover, **we found that cyclization of the peptides significantly increased the level of anti-peptide antibodies reacting with the intact antigen protein.** Deglycosylation increased the level of protein reactivity of anti-peptide antibodies and rendered the epitopes in peptides 5, 6, 10 accessible, which were masked in the native protein. Peptide 1 induced antibodies reacting only with the denatured reduced gp125 HIV-2. In addition, while anti-peptide L antibodies reacted better with L peptide (called "linear" structural specificity), anti-peptide C antibodies reacted similarly with L and C peptides (called "broad" structural specificity). Interestingly, the "broad" structural specificity of antibodies correlated with reactivity against native gp125. Although none of these anti-peptide antisera displayed neutralizing activity against HIV-2ROD, these results support the hypothesis that the structural restriction of peptides have a major influence upon the generation of more specific antibodies for recognizing the intact protein.

L28 ANSWER 40 OF 79 MEDLINE
1998005201 Document Number: 98005201. PubMed ID: 9346844. Cyclic peptides as conformationally restricted models of viral antigens: application to foot-and-mouth disease virus. Valero M L; Camarero J A; Adeva A; Verdaguer N; Fita I; Mateu M G; Domingo E; Giralt E; Andreu D. (Department of Organic Chemistry, University of Barcelona, Spain.) BIOMEDICAL PEPTIDES, PROTEINS AND NUCLEIC ACIDS, (1995) 1 (3) 133-40. Journal code: 9506699. ISSN: 1353-8616. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Conformationally restricted cyclic peptide mimics of the antigenic site A of foot-and-mouth disease virus serotype C-S8c1 have been designed, first by comparison to the three-dimensional structure of the O1BFS serotype, later more accurately on the basis of X-ray diffraction data from a complex between a linear peptide reproducing site A and an FMDV-derived monoclonal antibody Fab fragment. A variety of cyclization strategies have been attempted, both in solution and in the solid phase, involving disulfide, side chain lactam and head-to-tail arrangements. Preliminary immunological results have shown one of the cyclic disulfide mimics to be a better immunogen than its linear counterpart.